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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James R. LaDine et al. Art Unit : 1631
Serial No. : 09/835,273 Examiner : Michael L. Borin
Filed : April 13, 2001
Title : PROTEOMIC ANALYSIS BY PARALLEL MASS SPECTROMETRY

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

(1) Real Party in Interest

The real party in interest is Thermo Finnigan LLC, by virtue of an assignment from the inventors recorded in the U.S. Patent Office on January 7, 2002, November 29, 1999, Reel 012434, Frame 0382.

(2) Related Appeals and Interferences

There are no related appeals or interferences known to the appellant.

(3) Status of Claims

Claims 1-2, 5-18, 22-45 are rejected under 35 U.S.C. 103(a) as obvious over Demirev et al. (Analytical Chemistry (1997), 69(15), 2893-2900) or Chang et al. (US 4,507,555). Claims 3-4 and 19-21 are cancelled. No claims are allowed.

(4) Status of Amendments

There are no amendments filed subsequent to final rejection. All amendments were made prior to the final rejection.

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(5) Summary of Invention

In a first aspect, the invention features a method for analysis of proteins in a biological system. (e.g. 3:1-11[1]) The method includes providing a biological system, which is sampled at multiple time intervals to provide multiple samples, each sample containing multiple proteins. (e.g. 6:19-27; figure 1) The multiple samples are submitted to a separation technique to provide multiple protein samples suitable for analysis by mass spectrometry. (e.g. 7:3-5) The multiple samples are analyzed to determine changes in abundance of proteins as a function of time. (e.g. 7:21-26) The analysis includes allocating the multiple protein samples for the multiple samples among mass spectrometry systems in a parallel array of mass spectrometry systems. (e.g. 7:15-16, 7:26-8:3; figure 1) Each mass spectrometry system is adapted for protein analysis and provides mass spectral data indicating identity and abundance of one or more proteins. (e.g. 7:23-26; figures 3, 5) The analysis also includes directing the mass spectral data from each of the mass spectrometry systems in the array to a common computing device, and collating it as a function of time of sampling of the biological system. (e.g. 7:23-25; 8:3-12)

In another aspect (e.g. 3:12-23), the invention features a method for analysis of proteins in a biological system including: providing a biological system containing proteins (e.g. 6:20-21); exposing the biological system to a stimulus (e.g. 6:23-24; 14:12-24); after exposing the biological system to the stimulus, sampling the biological system at multiple time intervals to obtain multiple samples, each sample containing multiple proteins (e.g. 6:24-27); treating the multiple samples by a parallel separation technique to provide multiple protein samples suitable for analysis by mass spectrometry (e.g. 7:3-5); providing a parallel array of mass spectrometer systems capable of simultaneous analysis of as many protein samples as there are spectrometer systems in said array (e.g. 7:15-16, 7:26-8:3; figure 1); allocating the multiple protein samples among the mass spectrometry systems in the parallel array of mass spectrometry systems to obtain mass spectral data indicating identity and abundance of proteins in said multiple protein samples (e.g. 7:15-16, 7:23-8:3; figures 1, 3, 5); communicating the mass spectral data to a common computing device (e.g. 8:3-9); and collating said mass spectral data as a function of time (e.g. 7:23-28; 8: 10-12).

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[1] The notation X:y-z is used herein to refer to page X, lines y through z, of the specification.

In another aspect, the invention features a system for mass spectrometric analysis of proteins in a biological system. (e.g. 3:24-30) The system includes a parallel sample separation apparatus adapted to receive multiple samples of a biological system taken at multiple time intervals and separate the multiple samples in parallel to obtain multiple protein samples for analysis by mass spectrometry. (e.g. 6:19-27; 14:1-9; figure 4) The system also includes a parallel array of mass spectrometry systems adapted to receive the multiple protein samples from the separation apparatus and analyze the multiple protein samples in parallel to generate mass spectral data indicating identity and abundance of proteins. (e.g. 7:15-16, 7:26-8:3, figure 1) A computing device communicates with the parallel array of mass spectrometry systems and the parallel separation apparatus, and is adapted to analyze the mass spectral data from the parallel array of mass spectrometry systems and collate the mass spectral data as a function of time of sampling. (e.g. 7:23-25; 8:3-12)

In addition, embodiments can include one or more of the following. The separation technique includes use of one or more separation apparatus and the common computing device communicates with each of the separation apparatus. The separation technique includes use of an array of parallel separation apparatus. (e.g. figure 4) The array of separation apparatus treats multiple samples in parallel. (e.g. 8:19-22) The array of separation apparatus treats multiple samples in parallel and the array of mass spectrometry systems treats multiple samples in parallel. (e.g. figure 4) The number of separation apparatus in the array of parallel separation apparatus is equal to the number of mass spectrometry systems in the array of parallel mass spectrometry systems. (e.g. 14:1-9) A first portion of the multiple protein samples are allocated among the mass spectrometry systems before a second portion of the multiple protein samples have been provided by the separation technique. (e.g. 7:26-29) Treatment of multiple samples by the array of separation apparatus is carried out in parallel with treatment of multiple samples by the array of mass spectrometry systems. (e.g. 7:26-29)

(6) Issues

Are claims 1-2, 5-18, and 22-45 properly rejected under 35 U.S.C. § 103(a) as unpatentable over Demirev et al., Analytical Chemistry (1997), 69(15): 2893-2900 ("Demirev") or U.S. Patent No. 4,507,555 ("Chang")?

(7) Argument

1. Claims 1-2, 5-18, and 22-45

Claim 1, as finally rejected, recites a method for the analysis of multiple samples containing multiple proteins taken from a biological system at multiple time intervals. The samples are submitted to a separation technique and the resulting multiple protein samples are then allocated among mass spectrometry systems in an array of mass spectrometry systems. Each mass spectrometry system provides mass spectral data indicating identity and abundance of one or more proteins. A common computing device then collates the mass spectral data, for the multiple protein samples from the multiple samples, as a function of the time of sampling of the biological system.

The balance of the claims in group 1(a) also recite analysis of multiple samples containing multiple proteins taken from a biological system at multiple time intervals; an array of mass spectrometry systems, each system providing mass spectral data indicating identity and abundance of one or more proteins; and collating by a common computing device of mass spectral data from the array of mass spectrometry systems as a function of the time of sampling.

Neither Demirev nor Chang describes or suggests the use of an array of mass spectrometry systems, each system providing mass spectral data indicating identity and abundance of one or more proteins, let alone the use of an array of mass spectrometry systems for the analysis of multiple samples that have each been separated into multiple protein samples, as required by the pending independent claims.

Demirev describes statistics that can be used to characterize the diversity in a combinatorial library of peptides in a single sample, e.g. by calculating the mean and standard deviation of mass spectrometry signals generated for the combinatorial library of peptides. This "massively parallel" (p. 2900) approach characterizes a combinatorial or "parallel" library of peptides by the distribution of its mass spectral patterns instead of the possibly difficult-to-obtain identities of the constituents. It is not a method for analyzing the identities and abundances of proteins in multiple protein samples with a parallel array of mass spectrometers, as required by the pending independent claims.

Chang describes the use of a special mass spectrometry system to analyze a single sample. The system is referred to as a "parallel" mass spectrometer (PMS) because it has two or more sets of ion extraction means, mass resolution devices, and ion detectors that are connected in parallel rather than in tandem. This type of mass spectrometer provides for two simultaneous analyses of the components in a single sample. But there is no parallel array of mass spectrometry systems that analyzes multiple protein samples (each of which may have a plurality of components) from multiple samples, as required by the pending independent claims.

The Examiner states at page 7 of his Office Action of September 15, 2004, that the claims comprise steps of "separating multiple protein samples, analyzing them with parallel mass spectrometry and correlating mass spectrometry data as a function of time." That is not correct.

First, the "multiple protein samples" are not separated but, rather, are the *result* of a separation. What is separated are "multiple samples," which are taken from a biological system at multiple time intervals and have multiple proteins. Each of the multiple samples is separated into multiple protein samples, each of which must then be analyzed. Demirev and Chang each describe the analysis of multiple peptides or proteins, but they are all in a single sample, not in multiple protein samples as required by the claims.

Second, the multiple protein samples are not analyzed with "parallel mass spectrometry," which the Examiner says at page 3 is a "well known analytic technique." Rather, the multiple protein samples are allocated among mass spectrometry systems in *an array of mass spectrometry systems*. This explicit requirement of an array of mass spectrometry systems is simply not described by Demirev, Chang, or other authors who have alluded to the use of parallel mass spectrometry. Indeed, the Examiner acknowledged that applicant's previous arguments were "persuasive-in-part" and withdrew two previously cited references which alluded to "parallel" aspects of spectrometry but did not disclose a parallel array of mass spectrometry systems. Similarly, Demirev's mention of "parallel mass spectrometry" to describe the analysis of a parallel array of peptides is not a description of a parallel array of mass spectrometry systems as required by the claims. Chang's description of a mass spectrometer that has "parallel" components is also not a description of a parallel array of mass spectrometry systems, as required by the claims.

Third, and finally, the claims as previously amended require *collating* of the mass spectral data from the array of mass spectrometry systems as a function of time of sampling. (All of the claims except for claim 22 were amended to require "collating" instead of "correlating" of the mass spectral data; the applicant respectfully submits that the failure to so amend claim 22 was an oversight and, as appropriate, requests and authorizes such amendment to be made by an Examiner's amendment at the conclusion of the appeal process.) Such collating is necessitated by the allocation of multiple protein samples among the parallel array of mass spectrometers but is nowhere described or suggested in Demirev or Chang.

The Examiner asserts at page 3 that it would have been "prima facie obvious to one skilled in the art at the time the invention is made to apply parallel mass spectrometry to any problem requiring simultaneous measurement of plurality of biological samples, such as, for example, measurement of plurality of protein samples." But as discussed above, the claims call for the use of "an array of parallel mass spectrometers" – not "parallel mass spectrometry."

To the extent that the Examiner meant that it would have been obvious to one of skill in the art to create a parallel array of mass spectrometry systems and use it as specified in the claims, the applicant respectfully disagrees. There is simply nothing in the Examiner's analysis to support the whole cloth creation of such a system and its use as a modification to Demirev or Chang.

Demirev describes methods for the statistical analysis of the peptides in a single sample with a single mass spectrometry system and does not even attempt to identify the proteins or peptides in the sample. Chang merely describes a system with two or more sets of ion extraction means, mass resolution devices, and ion detectors that permits two different and simultaneous analyses of a single sample. The Examiner provides no indication of the feasibility or desirability of modifying Demirev's statistical method or Chang's system having double components to include the use of *a parallel array of mass spectrometers to analyze identity and abundance of proteins in multiple protein samples*, as required by the claims.

The applicant recognizes that a rationale for combining or modifying references can be implied or reasoned from the prior art or from knowledge generally available to one of ordinary skill in the art. The applicant further recognizes that it is proper to take into account the inferences that one of skill in the art would reasonably be expected to draw from a reference, as

noted by the Examiner at page 5. But the elements of the claims are not even described in the cited references, and the Examiner has provided no line of reasoning and no basis for inferring the claimed invention from the description of mass spectrometry systems and the idea of parallel analysis represented in the cited references.

In the absence of a convincing line of reasoning, the only basis for such a drastic modification to Demirev or Chang is the hindsight provided by applicant's claims – and the use of hindsight to establish a prima facie case of obviousness is simply not proper. See *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985); *In re Dembiczak,* 175 F.3d 994 (Fed. Cir. 1999) *abrogated on other grounds in In re Gartside,* 203 F.3d 1305 (Fed. Cir. 2000) (noting the "subtle but powerful attraction of a hindsight-based obviousness analysis" and requiring a "rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references); MPEP 2142, paragraph 2.

Moreover, the Board of Appeals cannot simply rely on the Examiner's knowledge or its own knowledge as skilled artisans. There must be an evidentiary record that demonstrates the presumed knowledge and establishes the obviousness of the invention. *In re Kotzab,* 217 F.3d 1365, 1371 (Fed. Cir. 2000) ("[P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed."); see also *In re Lee*, 277 F.3d 1338, 1343, 1345 (Fed. Cir. 2002) ("[When relying on] general knowledge to negate patentability, that knowledge must be articulated and placed on the record.") There is no such record here.

Because Demirev and Chang both fail entirely to disclose or suggest an array of mass spectrometry systems, each system providing mass spectral data indicating identity and abundance of one or more proteins; because Demirev and Chang both fail to disclose or suggest the use of an array of mass spectrometry systems for the analysis of multiple samples that have each been separated into multiple protein samples; because Demirev and Change both fail to disclose or suggest collating of data from such an analysis; and because the Examiner has provided no factual or logical basis for modifying Demirev and/or Chang to have such features, the applicant respectfully submits that no prima facie case of obviousness under 35 U.S.C. § 103 has been established with respect to these claims.

Accordingly, the applicant submits that all of the pending claims are in condition for allowance.

2. Claims 8, 10-11, 29-42

In addition, claims 8, 10-11, 29-42 are separately patentable from the balance of the pending claims. Claim 8 depends from claim 1, and further specifies that the separation technique includes use of one or more separation apparatus and said common computing device communicates with each of said separation apparatus. Thus, in addition to requiring analysis of multiple samples containing multiple proteins taken from a biological system at multiple time intervals; an array of mass spectrometry systems, each system providing mass spectral data indicating identity and abundance of one or more proteins; and collating by a common computing device of mass spectral data from the array of mass spectrometry systems as a function of the time of sampling, claim 8 also requires one or more separation apparatus that communicate with the common computing device. Claim 10-11 and 29-42 have similar requirements and the arguments presented here apply equally to them.

The Examiner did not address claim 8 separately from the other claims and did not indicate whether or where Demirev or Chang disclosed the limitation of claim 8. Indeed, neither Demirev nor Chang disclose or suggest the use of one or more separation apparatus that communicate with a common computing device. The applicant therefore respectfully submits that no prima facie case of obviousness under 35 U.S.C. § 103 has been established with respect to claim 8. Claims 10 and 38-40 incorporate the features of claim 8 and are allowable for at least the reasons set forth for claim 8. Claim 29, like claim 39 (which depends from claim 8) requires a parallel sample separation apparatus, which of necessity includes more than one separation apparatus and is therefore also allowable for at least the reasons set forth for claim 8.

(8) Appendix

Appendix A to this brief is a set of the claims currently pending in this case.

The brief fee of $500 is enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: March 18, 2005

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Appendix A

Listing of Claims:

1. (Previously presented) A method for analysis of proteins in a biological system comprising:

providing a biological system;

sampling the biological system at multiple time intervals to provide multiple samples, each sample containing multiple proteins;

submitting each of the multiple samples to a separation technique to provide multiple protein samples suitable for analysis by mass spectrometry; and

analyzing the multiple samples to determine changes in abundance of proteins as a function of time, said analyzing including

allocating the multiple protein samples for the multiple samples among mass spectrometry systems in a parallel array of mass spectrometry systems, each mass spectrometry system adapted for protein analysis and providing mass spectral data indicating identity and abundance of one or more proteins,

directing mass spectral data from each of the mass spectrometry systems in said array to a common computing device, and

collating said mass spectral data from each of the mass spectrometry systems as a function of time of sampling of the biological system.

2. (Previously presented) The method of claim 1 further comprising displaying said collated data as a function of protein identity, protein abundance, and time.

3. (Canceled)

4. (Canceled)

5. (Previously presented) The method of claim 1 wherein said array of mass spectrometry systems includes at least 5 mass spectrometers.

6. (Previously presented) The method of claim 1 wherein analyzing the multiple samples includes analyzing the multiple samples to determine changes in abundance of 500 proteins or more.

7. (Previously presented) The method of claim 1 wherein analyzing the multiple samples includes analyzing the multiple samples to determine changes in abundance of about 5000 proteins or more.

8. (Previously presented) The method of claim 1 wherein the separation technique includes use of one or more separation apparatus and said common computing device communicates with each of said separation apparatus.

9. (Previously presented) The method of claim 1 wherein the separation technique includes use of liquid chromatography.

10. (Previously presented) The method of claim 8 wherein the separation apparatus includes a magnetic particle separation apparatus.

11. (Previously presented) The method of claim 38 wherein the array of separation apparatus treat multiple samples in parallel.

12. (Previously presented) The method of claim 1 wherein the separation technique includes treating each of the multiple protein samples with a protease to produce peptides and the mass spectral data includes amino acid sequence data that can be compared to amino acid sequence data derived from a data base.

13. (Previously presented) The method of claim 12 wherein said mass spectrometry systems are LC-TMS mass spectrometers.

14. (Previously presented) The method of claim 1 further comprising:

exposing a first instance of the biological system to a stimulus and maintaining a second instance of the biological system free of the stimulus;

wherein sampling, submitting, and analyzing include sampling, submitting, and analyzing each of the first and the second instances; and

correlating mass spectral data includes comparing mass spectral data from the first and the second instances.

15. (Original) The method of claim 14 comprising separately analyzing samples from said first component and second component.

16. (Previously presented) The method of claim 43 wherein the perturbation results from exposure of the biological system to heat, light, cold, motion, agitation, cellular material, or a drug.

17. (Previously presented) The method of claim 1 wherein the time interval is about 5 to 60 seconds.

18. (Previously presented) The method of claim 1 wherein the time interval is about one minute to one hour.

Claims 19-21. (Cancelled)

22. (Previously presented) A method for analysis of proteins in a biological system comprising:

providing a biological system containing proteins;

exposing the biological system to a stimulus;

after exposing the biological system to the stimulus, sampling the biological system at multiple time intervals to obtain multiple samples, each sample containing multiple proteins;

treating the multiple samples by a parallel separation technique to provide multiple protein samples suitable for analysis by mass spectrometry;

providing a parallel array of mass spectrometer systems capable of simultaneous analysis of as many protein samples as there are spectrometer systems in said array;

allocating the multiple protein samples among the mass spectrometry systems in the parallel array of mass spectrometry systems to obtain mass spectral data indicating identity and abundance of proteins in said multiple protein samples;

communicating the mass spectral data to a common computing device; and

correlating said mass spectral data as a function of time.

23. (Previously presented) The method of claim 22 wherein the parallel separation technique is performed using a parallel magnetic particle separation device.

24. (Previously presented) The method of claim 23 wherein the parallel array of mass spectrometry systems includes an array of LC-MS spectrometer systems.

25. (Previously presented) The method of claim 24 wherein the array includes 6-20 mass spectrometers.

26. (Previously presented) The method of claim 25 wherein the time intervals are in the range of 5 seconds to 10 minutes.

27. (Previously presented) The method of claim 26 wherein the analysis includes analysis of about 500 proteins or more.

28. (Previously presented) The method of claim 23 wherein the central computer communicates with the parallel magnetic particle separation device.

29. (Previously presented) A system for mass spectrometric analysis of proteins in a biological system, the system comprising:

a parallel sample separation apparatus adapted to receive multiple samples of a biological system taken at multiple time intervals, and separate the multiple samples in parallel to obtain multiple protein samples for analysis by mass spectrometry;

a parallel array of mass spectrometry systems adapted to receive the multiple protein samples from the separation apparatus and analyze the multiple protein samples in parallel to generate mass spectral data indicating identity and abundance of proteins; and

a computing device communicating with the parallel array of mass spectrometry systems and the parallel separation apparatus, the computing device being adapted to analyze the mass spectral data from the parallel array of mass spectrometry systems and collate the mass spectral data as a function of time of sampling.

30. (Previously presented) The system of claim 29, wherein the parallel separation device is a parallel magnetic particle separation device.

31. (Previously presented) The system of claim 29, wherein the parallel separation device is a parallel chromatography separation device.

32. (Previously presented) The system of claim 29, wherein the computing device is adapted to collate the mass spectral data as a function of time.

33. (Previously presented) The system of claim 29, further comprising a graphical user interface that can be searched, queried, or filtered to display selected collated data.

34. (Previously presented) The system of claim 29 wherein the parallel array of mass spectrometry systems includes at least 5 mass spectrometers.

35. (Previously presented) The system of claim 29, wherein the parallel array of mass spectrometry systems includes at least 20 mass spectrometers.

36. (Previously presented) The system of claim 29, wherein the parallel array of mass spectrometry systems is adapted to generate mass spectral data including peptide fragment mass spectra, and the computing device is adapted to analyze the mass spectral data in conjunction with an amino acid sequence derived from a database.

37. (Previously presented) The system of claim 29, wherein the parallel array of mass spectrometry systems include a liquid chromatograph-tandem mass spectrometer system.

38. (Previously presented) The method of claim 8 wherein a first portion of the multiple protein samples are allocated among the mass spectrometry systems before a second portion of the multiple protein samples have been provided by the separation technique.

39. (Previously presented) The method of claim 8 wherein the separation technique includes use of an array of parallel separation apparatus.

40. (Previously presented) The method of claim 39 wherein the number of separation apparatus in the array of parallel separation apparatus is equal to the number of mass spectrometry systems in the array of parallel mass spectrometry systems.

41. (Previously presented) The method of claim 11 wherein the array of mass spectrometry systems treat multiple samples in parallel.

42. (Previously presented) The method of claim 41 wherein treatment of multiple samples by the array of separation apparatus is carried out in parallel with treatment of multiple samples by the array of mass spectrometry systems.

43. (Previously presented) The method of claim 1 further comprising exposing the biological system to a perturbation, wherein sampling of the biological system occurs at multiple time intervals after the exposure of the biological system to the perturbation.

44. (Previously presented) The method of claim 1 further comprising inferring interactions over time between and among proteins in the biological system.

45. (Previously presented) The method of claim 2 wherein protein abundance is expressed as relative abundance of proteins in each of the multiple samples.

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SUBMISSION OF APPEAL BRIEF

Further to the Notice of Appeal filed on January 14, 2005, and received in the U.S. Patent Office on January 18, 2005, the Applicant submits herewith an Appeal Brief, and a check in the amount of $500.00 for the Appeal Brief fee.

Respectfully submitted,

Date: March 18, 2005

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